Postgraduate Medical Journal (May 1970) **46**, 314–317.

CURRENT SURVEY

Hypnotic drugs

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THIS review will treat the more commonly prescribed hypnotic agents and their sleep-inducing properties. Hypnotic agents that are seldom used (paraldehyde), drugs that are not singularly soporific but may be used either alone or as adjuncts in inducing sleep [e.g. meprobamate (Equanil, Miltown), chlordiazepoxide (Librium) and diazepam (Valium)] and drugs that have little soporific effect [antihistamines, bromides and methylparafynol (Oblivon, Dormison) (Lasagna, 1954)] will not be discussed.

Indications

Insomnia is an extremely common complaint with which physicians are perpetually confronted. Many patients have chronic insomnia. In other patients insomnia is acute but intermittent. Situations in which acute insomnia can occur are during or after plane or train travel, hospitalization in strange and often noisy surroundings or simply having to sleep in environments that are different or unfamiliar.

There appear to be three basic types of insomnia. In one type a person has difficulty only in falling asleep. In a second type, individuals achieve sleep easily, but have trouble staying asleep. In a third type, both falling *and* remaining asleep are physiologically arduous.

Let us emphasize that chronic insomnia is best treated by attacking the underlying cause, if apparent. If not evident, the cause (or causes) should be carefully sought by the physician. Lack of sleep associated with somatic pain or with a psychiatric problem, for example, may be treated best by prescribing analgesics, or tranquilizers and/or psychotherapy.

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Human pharmacology

In the past, hypnotics have been divided into barbiturates and non-barbiturates. This classification, based on chemical structure, has little contemporary clinical significance since compounds in each group have essentially the same qualitative pharmacologic properties. Naturally, there are quantitative differences in onset and duration of action.

Onset of action

Onset is generally rapid with liquid preparations such as syrup of chloral hydrate (Noctec, Somnos), elixir of pentobarbital (Nembutal) and elixir of secobarbital (Seconal). However, liquids are not as convenient as capsules and since a capsule of sodium secobarbital, sodium pentobarbital or chloral hydrate usually causes drowsiness within about 30 min, these three compounds give quite satisfactory hypnotic results in most patients in capsular form.

Onset of action is also related to the intrinsic pharmacodynamic nature of the particular hypnotic agent. An 'ultra-short acting' barbiturate such as hexobarbital (Sombulex, Cyclonal) probably has the most prompt onset of action while a 'long-acting' barbiturate such as phenobarbital may require several hours to produce maximal effect (Sharpless, 1965a). The reasons for the variability of pharmacodynamic (and thus biochemical) behaviour among the various hypnotic agents is beyond the scope of this review (see Shideman, 1961; Sharpless, 1965a, b).

Duration of action

Duration of hypnotic effect is largely dependent on two factors, the intrinsic pharmacodynamic characteristics of the drug and the dosage used.

Both of these factors should be considered when selecting a hypnotic agent. If a patient requires a drug with a rapid but brief hypnotic effect, perhaps one of the 'ultra-short acting' barbiturates, ordinarily used as intravenous anaesthetics, may be useful. Bush, Berry & Hume (1966) studied oral sodium hexobarbital (Sombulex, Cyclonal), sodium methohexital and sodium thiopental (no oral preparations of the latter two drugs are commercially available) and their results indicate that these three drugs may be useful in treatment of patients who have difficulty in falling asleep but who, once asleep, do not easily awaken.

If a patient needs a hypnotic for both inducing *and* maintaining sleep, one of the longer acting hypnotics *in an appropriate dose* is indicated. In most patients a 1·0 g dose of chloral hydrate, for example, will provide adequate sleep but doses of 1·5 g or 2·0 g may be necessary in some patients.

The older designations of hypnotics as being 'short-acting', 'medium-acting', 'long-acting', are clinically and pharmacodynamically meaningless. Such labels have no scientific meaning because there are no valid human data to support them. No controlled human studies have been done, showing that specified doses of several hypnotics have different durations of action. Thus, commercial preparations combining a 'short-acting' barbiturate with a 'moderately long-acting' barbiturate (as in Tuinal) are not pharmacologically rational. By increasing or decreasing the dosage of such a drug as secobarbital, for instance, the physician can usually obtain any effect from relatively brief and shallow sedation to a prolonged and rather profound coma-like state.

Dose variability

The dose required for a satisfactory hypnotic effect varies greatly among individual patients. Such variability can be explained in part by individual differences in the metabolism of a drug or in the response of individual central nervous systems to a given concentration of the drug. But the necessary dose is also related to other differences in a patient's condition, such as the degree of anxiety or depression present, and to the environment in which he must sleep. Thus, the use of a 'standard' dose under all circumstances is not rational (or efficacious) therapeutics. A patient should first receive a relatively low dose of a hypnotic (e.g. 0·5 g of chloral hydrate or 50 mg of secobarbital or pentobarbital). If hypnosis is not achieved, the dose may be doubled or even tripled. It is generally better therapeutics to adjust the dose of a specific drug with which the physician is familiar to the individual requirements of the patient than to try other drugs.

Side-effects

Paradoxical mental excitement reportedly occurs in some persons following administration of a barbiturate. However, such an effect appears to be a rather rare phenomenon. It is said to occur less frequently with chloral hydrate than with the barbiturates. Similarly, the alleged capacity of hypnotics to produce delirium in patients with pain is rarely evident clinically. There seems to be little reason to avoid prescribing hypnotics for patients in pain who also have insomnia. Of course, appropriate analgesics should also be prescribed.

Gastric irritation is said to be a problem with chloral hydrate but modern dosage forms (capsules, syrup) appear to have largely eliminated this side effect. Chloral betaine (Beta-Chlor), a relative of chloral hydrate, is said to cause less gastric irritation but there is no objective evidence to support this claim.

Hangover, or residual sedation after waking, is a problem with many of the hypnotics although in some patients, e.g. certain hospitalized persons, this effect may not be undesirable. The only hypnotics not having this side-effect are the 'ultra-short acting' barbiturate hexobarbital (Sombulex, Cyclonal) and, for most persons, the non-barbiturate compound ethinamate (Valmid). Other barbiturates, although called 'short-acting', are all known to have this side effect. The non-barbiturates methyprylon (Noludar), ethchlorvynol (Arvynol, Serenesil, Placidyl), methaqualone (Quaalude, Melsed, Melsedin, Paxidorm) and glutethimide (Doriden), have this side-effect in some persons, also; there are no well-designed studies demonstrating their lack of hangover. With all hypnotics hangover can be minimized by titrating each patient's insomnia against different doses of a particular drug.

Various allergic reactions have been noted with the use of all hypnotics. The symptoms usually are skin rash, pruritus, nausea and vomiting.

More serious adverse effects have been encountered. The Registry on Adverse Reactions of the American Medical Association has received a number of reports of reactions to hypnotic drugs (see Table 1). A direct causal relationship was not definitely established because these reports come from a variety of sources not subject to follow-up investigation. The reports may represent only a fraction of the reactions which do occur.

In addition to the unpublished Registry reports, adverse reactions have also been reported in the literature. Two cases of peripheral neuropathy due to glutethimide were reported by Bartholomew (1961). Cases of thrombocytopenia following the use of ethinamate have been reported (Sharpless, 1965b). Methaqualone has been cited as a possible cause of aplastic anaemia (New Drugs, 1967).

Acute intoxication or poisoning with the hypnotics is common. It has been estimated that there are

TABLE 1. Reported associations with adverse reactions to hypnotic agents

Drug	Reaction	No. of cases
Glutethimide	Urticaria	5
	Exanthematic rash	17
	Peripheral neuropathy, haematuria, weakness, slurred speech, mental decline, thrombocytopenia, aplastic anaemia with pancytopenia, leukopenia, megaloblastic anaemia, agranulocytosis, allergic dermatitis	1 or 2
Ethinamate	Macular rash	1
Pentobarbital	Leukopenia	3
	Exanthematic rash	14
	Jaundice	8
	Dyspnea (cyanotic), thrombocytopenia, haemolytic anaemia, psychoses, agitation, extrapyramidal reactions, seizures, urticaria	1 or 2
Secobarbital	Leukopenia	4
	Extrapyramidal reactions	3
	Urticaria	3
	Exanthematic rash	16
	Jaundice	4
	Aplastic anaemia, thrombocytopenia, seizures, neuropathy, confusional state, erythema multiforme	1 or 2
Methyprylon	Agranulocytosis	1
Ethchlorvynol	Numbness of arms, seizures, aplastic anaemia with pancytopenia, leukopenia, itching and skin rash, liver abnormalities	1 or 2
Chloral hydrate	Urticaria	3
	Exanthematic rash	7
Methaqualone	Paresthesias, abdominal pain, dilated pupils	1

The above data are unpublished information from the Registry on Adverse Reactions of the Council on Drugs of the American Medical Association.

15,000 barbiturate poisonings in the United States every year. The signs and symptoms of barbiturate poisoning are chiefly referred to the central nervous and the cardiovascular systems. For appropriate treatment of poisoning the reader is referred to other sources for detailed information (Arena, 1967; Done, 1969; Gleason *et al.*, 1969).

Tolerance and dependence

Tolerance to, and physical dependence upon, barbiturates and most non-barbiturates have been noted. It is not known if tolerance to hypnotics in ordinary night-time doses is a significant problem. Sharpless (1965a) feels that it is and he advises caution in prescribing hypnotics for patients with chronic insomnia. He believes that in such cases the possible consequences of persistent insomnia must be weighed against the possible dangers of the regular and habitual use of hypnotic drugs. 'No general rule can be given. The danger of *severe* physical dependence and addiction is overemphasized; more pertinent is the question whether regular use of barbiturates and other hypnotics may not tend to obscure or exacerbate the condition underlying the insomnia, thus establishing a vicious cycle in which the patient becomes psychologically dependent on or "habituated" to, the drug' (Sharpless, 1965a).

To be truly addicted to a hypnotic agent, that is physiologically dependent, one must take large doses over a long period of time (Shideman, 1961). The large dose requirement distinguishes the hypnotics from the opiates. Thus, the use of therapeutic doses of a barbiturate for a period of years will not produce addiction ordinarily.

Interaction

Many agents are known to interact with hypnotics to produce a greater degree of physiological depression than would be obtained with a hypnotic alone. Among such interacting compounds are alcohol, calcium salts, tranquilizers, mephenesin (Myanesin, Tolserol), and thiamine (Shideman, 1961). The exact physiological and biochemical nature and causes of these interactions are not understood. Patients who regularly take hypnotics are often taking daytime sedatives or some of the other agents mentioned above. Together, they probably can lead to physiologic dependence. Lasagna (1967) cautions against stopping all drugs suddenly and completely in such patients since an abstinence syndrome (or 'withdrawal syndrome') can rapidly and fulminantly occur. The patient's drug intake should be slowly reduced at the rate of 100 mg secobarbital-equivalent/day.

Hypnotics can also prolong the action of other

non-hypnotic drugs. An example is methaqualone's prolongation of the action of methscopolamine (*New Drugs*, 1967).

Contraindications

The barbiturates are completely contraindicated in patients with a personal or familial history of acute intermittent porphyria, because these drugs stimulate certain liver enzymes that can cause a precipitous and dangerous rise in the level of porphyrins. Several of the barbiturates and chloral hydrate are known to cross the placental barrier readily and are found in foetal tissue. If hypnotics are considered for administration to pregnant women, the possibility of risk of foetal respiratory and central nervous system depression must be carefully weighed against the expected therapeutic benefits to the mother. All hypnotics should be administered with caution and initially in reduced doses to patients with hepatic damage. The specific dangers ascribed to use of barbiturates and chloral hydrate in patients with hepatic disease seem to have been over-emphasized in the past. The traditional textbook caution concerning chloral hydrate's use in cardiac patients has not been justified by actual clinical experience (Medical Letter, 1960).

For more complete information on side-effects, toxicity, interactions and contraindications, the reader is referred to the product literature for the drug in which he is interested. In general, much less is known about the pharmacology and toxicology of the non-barbiturates.

Conclusions

There are few objective data on which to base a recommendation of drugs of choice for insomnia, because there is a remarkable paucity of well-designed comparative clinical studies showing that a given hypnotic agent is more effective and has fewer side-effects than other hypnotic agents. With few exceptions, there is little difference between the ability of the various hypnotic agents to depress the central nervous system, and the agents vary only in their onset and duration of action and the dosage required to produce sleep. The incidence of side-effects appears to be approximately equal for all hypnotic agents, although clinical experience seems to indicate that the most troublesome side-effect, hangover, is lower with chloral hydrate than with all of the other agents (*not including* the 'ultra-short acting' barbiturate hexobarbital).

For patients who need a hypnotic only to help them get to sleep, hexobarbital is a useful drug. Unfortunately, there has been little clinical experience with this drug. Ethinamate is another compound that acts rapidly (about 30 min) and only for a relatively short time (about 3–4 hr).

Our choice of a hypnotic agent for patients who need a drug both to fall *and* stay asleep is either chloral hydrate, pentobarbital or secobarbital. Of these three drugs, we have a slight preference for chloral hydrate because it appears less likely to cause tolerance and dependence, and to have a lower incidence of side-effects, particularly hangover. Secobarbital and pentobarbital seem to be indistinguishable from each other in almost every pharmacologic or pharmacodynamic respect. When prescribing any of these three drugs, adequate dosage should be used. With chloral hydrate, 1·5 or 2·0 g are often required. Owens & Marshall (1955) have shown that the usual adult dose—1·0 g—may be inadequate for some persons. With secobarbital and pentobarbital, the usual dose is 100 mg; however, 150 and 200 mg doses may be necessary in some patients.

We do not recommend the newer non-barbiturates because little is known about their pharmacology and toxicology. Some workers (and pharmaceutical manufacturers) have claimed that these drugs have a lower incidence of side-effects and a lower addiction potential than the barbiturates but such claims have not been conclusively verified. All of the non-barbiturate drugs are also more expensive than chloral hydrate, secobarbital or pentobarbital, particularly when any of these three drugs are prescribed by generic name.

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